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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/462,576	05/25/2000	DAPHNA HAVKIN-FRENKEL	13253-00001	5251

7590 08/11/2003

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EXAMINER

COLLINS, CYNTHIA E

ART UNIT	PAPER NUMBER
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1638

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DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/462,576

Applicant(s)

HAVKIN-FRENKEL ET AL.

Examiner

Cynthia Collins

Art Unit

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 May 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 31-34 and 41-43 is/are pending in the application.
- 4a) Of the above claim(s) 41-43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 31-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 41-43 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

Art Unit: 1638

DETAILED ACTION

The amendment filed on May 27, 2003, has been entered.

Claims 1 and 31-32 are newly amended.

Claims 41-43 are newly added.

Claims 1-7, 31-34 and 41-43 are pending.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Newly submitted claims 41-43 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 41 -43 are directed to a cell culture medium for the production of vanillin in cultured *Vanilla planifolia* cells. Group I, claims 1-11, directed to a first product (cultured *Vanilla planifolia* cells) and a first method of making said product (a method for improving production of vanillin in cultured *Vanillin planifolia*) was originally elected for prosecution in the reply filed July 5, 2001. Cell culture medium is a product distinct from the originally elected cultured *Vanilla planifolia* cells.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 41-43 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

Claims 1-7 and 31-34 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing vanillin in cultured *Vanilla planifolia* cells by supplementing the culture with 3% malic acid alone, 1 mM 3,4-dihydroxybenzaldehyde alone, or 30 ug/mL glycosylated lysozyme elicitor protein alone, does not reasonably provide enablement for a method for producing vanillin in cultured *Vanilla planifolia* cells by supplementing the culture with other combinations of compounds or other supplements, for the reasons of record set forth in the office action mailed January 27, 2003.

Applicant's arguments filed May 27, 2003, have been fully considered but they are not persuasive.

Applicants argue that the examples do not limit the teachings of the disclosure, and that the claims are fully enabled in view of the amendments. Applicants also argue that the Office improperly imposes a more exacting standard than is required under the statute, and that the previous office action is read as requiring that the effect of each particular concentration within a range or combination be set forth in the specification (reply pages 11-12).

The Examiner maintains that the previous office action does not require that the effect of each particular concentration within a range or combination be set forth in the specification. The Examiner also maintains that the disclosure of only three working examples, each illustrating the effect of a single concentration of a single compound on the production of vanillin by cultured *Vanilla planifolia* cells does not provide sufficient guidance for one skilled in the art to determine, without undue experimentation, how much and what combination of the recited elicitors to add to cultured *Vanilla planifolia* cells in order to achieve the desired effect, because

Art Unit: 1638

neither the prior art nor the specification discloses the effect of a representative number of concentrations and combinations within the claimed ranges and combinations.

Applicants further argue that the Office apparently adopts general conclusions based on the post-filing date review article by Rao et al. and interprets these broad generalizations as establishing unpredictability in the relevant art. Applicants argue that unpredictability with respect to the claimed methods and compounds cannot be premised on the unpredictability of any compound, and that Rao et al. is not relevant because Applicants' method does not vary phytohormone levels. Applicants also argue that even assuming some level of unpredictability, all Wands factors need be considered when evaluating enablement, and that in view of the high level of skill in the art, the working examples and teachings disclosed in the specification, combined with the ease with optimizing simple additions to culture medium can be achieved and the simplicity of assaying the effects of compounds on vanillin production, one skilled in the art could practice the claimed invention without undue experimentation (reply pages 12-13).

The Examiner reiterates that although the cited reference of Rao et al. was published after the effective filing date of the instant application, Rao et al. does provide evidence of what one skilled in the art would have known on or before the effective filing date, as Rao et al. is a review article that contains a summary of studies, some of which are directed to biotechnological methods for the production of vanillin using *Vanilla planifolia* cell cultures. The summarized studies directed to biotechnological methods for the production of vanillin using *Vanilla planifolia* cell cultures were published before the effective filing date of the instant application. The Examiner also maintains that the cited reference of Rao et al. is neither broad nor general.

Art Unit: 1638

Rao et al. is specifically directed to the production of vanillin using *Vanilla planifolia* cell cultures, and to the effect of various compounds, including phytohormones and vanillin precursors, on vanillin production by cultured *Vanilla planifolia* cells. The Examiner further maintains that unpredictability with respect to the claimed methods and compounds can be premised on the unpredictability of the effects of other compounds on vanillin production by cultured *Vanilla planifolia* cells. The Examiner reiterates that while Applicants' method does not vary phytohormone levels, Applicant's method does employ 3,4-dihydroxybenzaldehyde, which is considered to be the immediate precursor of vanillin (specification, page 12, lines 31-33), and that while Rao et al. do not refer to 3,4-dihydroxybenzaldehyde specifically, Rao et al. do refer to the unpredictability of using other vanillin precursors on vanillin production by cultured *Vanilla planifolia* cells. The Examiner does not dispute that all Wands factors need be considered when evaluating enablement, or that the level of skill in the art is high, but maintains that the disclosure does not enable the full scope of the claims. In light of the unpredictability of the effect of different compounds on the production of vanillin in cultured *Vanilla planifolia* cells, and the lack of guidance with respect to which concentrations and combinations of compounds within the claimed ranges would affect vanillin production, it would require undue experimentation for one skilled in the art to practice the claimed invention. The Examiner maintains that the undue experimentation lies not in adding the compounds to the culture medium or in assaying the effects on vanillin production, which are within the abilities of one skilled in the art. The undue experimentation lies in the trial and error selection of compounds, combinations, and amounts prior to their addition to the cultured cells that would be required to

Art Unit: 1638

determine which compounds, combinations, and amounts would affect vanillin production in the desired manner and which would not.

Applicants additionally point to the submitted reference by Yin et al. (Nucleic Acids Research, 1996, Vol. 24, pages 1279-1286), teaching and using in biological research incomplete factorial design and response surface methods for experimental design as evidence that statistical-based experimental designs are routine in the biological sciences. Applicants argue that they need not teach what is well known in the art, and that the experimentation required to optimize a particular combination with well-defined ranges of elicitors is only routine (reply page 13).

The Examiner maintains that the submitted reference by Yin et al. is not germane to the instant rejection. First, Applicants do not appear to employ statistical-based experimental design for determining which and how much elicitor to add to a *Vanilla planifolia* culture in order to obtain the desired results. Second, Yin et al. employ statistical-based experimental design to evaluate the effect of different variables on the yield of tRNA in vitro system in which relevant variables are limited in number and more easily identified and controlled, whereas Applicants utilize an in vivo system in which relevant variables are more numerous and may be more difficult to identify and control.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1638

Claim 1, and claims dependent thereon, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite in the recitation of "at a concentration of at least about 0.01% by weight of the culture medium". The metes and bounds of the amount of compound used to supplement the culture are unclear, as the claim places no upper limit on the percent by weight of compound to be added to the culture.

Claim Rejections - 35 USC § 102

Claims 31-32 and 34 remain rejected under 35 U.S.C. 102(b) as being anticipated by Knuth et al. (US 5,057,424, 15 October 1991, Applicant's IDS), for the reasons of record set forth in the office action mailed January 27, 2003.

Applicant's arguments filed May 27, 2003, have been fully considered but they are not persuasive.

Applicants argue that claims 31-32 and 34 are directed to novel compositions. In response to the citation of *In re Thorpe*, Applicants argue that the claims provide a simple and straightforward way of distinguishing prior art cell culture compositions from those claimed, namely the claimed cultures are supplemented with an elicitor and have the ability to produce two or ten times the amount of vanillin as an equivalent culture without supplementation. Applicants further argue that claims 31-32 and 34 as currently amended are not product-by-process claims, and that it is proper to claim compositions of cell cultures in the comparative language used. Applicants argue that, unlike the claims at issue in *In re Thorpe*, they have claimed a cell culture composition supplemented with an elicitor, subject to the further limitation

Art Unit: 1638

of producing two or ten times the amount of vanillin as an equivalent culture without supplementation, and that while claims 9 and 10 were directed to cells produced by a particular method, no such limitation can be read into claims 31-32 and 34. Applicants further argue that whereas the production of the claimed cells by a particular process would be properly anticipated by cells having the required basic limitation, here the further limitation relating to the increase in the production of vanillin at day 15 of culture in no way constitutes a limitation referring to the method by which such cells are treated or prepared, but rather adds a required characteristic which one skilled in the art would understand and would recognize that the inventors were in possession of such cultures. Applicants argue that the claims as amended are not anticipated by Knuth et al. because Knuth et al. do not teach each and every limitation of the claimed invention expressly or inherently; in particular, Knuth et al. do not teach cell cultures comprising *Vanilla planifolia* in a culture media supplemented according to the claims and which produce at day 15 the amount of vanillin indicated (reply pages 6-7).

The Examiner acknowledges the amendment of the claims, now drawn to cell culture compositions comprising *Vanilla planifolia* cells in a culture medium supplemented with a specific elicitor of vanillin synthesis, which provides a way of distinguishing prior art cell culture compositions from those claimed. The rejection is maintained, however, because Knuth et al. teach a cell culture comprising root tip *Vanilla planifolia* cells supplemented with malic acid (columns 13-14 Example 2). While Knuth et al. do not explicitly teach the amount of vanillin produced after 15 days in culture, the cells taught by Knuth et al. would inherently produce the same amount of vanillin after 15 days in culture as the claimed cells, because the rejected claims require only that the cell culture medium be supplemented with malic acid, and that the cells be

Art Unit: 1638

root cells. Because the claimed supplemented cell culture medium is indistinguishable from the supplemented cell culture medium taught by Knuth et al, and because the claimed cell source is indistinguishable from the cell source by Knuth et al, the cells taught by Knuth et al. would necessarily produce the same amount of vanillin after 15 days in culture as the claimed cells.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Remarks

No claim is allowed.

Art Unit: 1638

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (703) 605-1210.

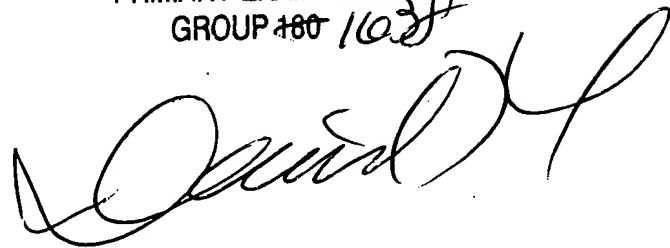
The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CC
August 5, 2003

DAVID T. FOX
PRIMARY EXAMINER
GROUP 180 11038

A large, stylized handwritten signature in black ink, likely belonging to David T. Fox, is written over the typed name and title.